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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,110	02/24/2005	Qishou Xu	CU-4057 BWH	3549

26530 7590 01/21/2010

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EXAMINER	
GOON, SCARLETT Y	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
01/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,110	XU ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2009 and 12 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,12 and 21-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8,12 and 21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 26 October 2009 in which claims 2-5, 9-11 and 13-20 were previously cancelled, claim 22 is amended to change the scope and breadth of the claims, claims 23-33 are amended to correct for formality issues related to claim numbering, and new claim 34 is added.

The Declaration of Mr. Xu Qishou (inventor), submitted by Applicant on 12 January 2010 under 37 CFR § 1.132, are acknowledged and will be further discussed below.

Claims 1, 6-8, 12 and 21-34 are pending in the instant application and are examined on its merits herein.

Priority

This application is a National Stage entry of PCT/CN03/00609 filed on 29 July 2003 and claims priority to China foreign application 02125917.8 filed on 2 August 2002. A certified copy of the foreign priority document in Chinese has been received. No English translation has been received.

Objections Withdrawn

Applicant's amendment, filed 26 October 2009, with respect to the objection of the claims for being misnumbered due to duplicate use of claim number 22, has been fully considered and is persuasive because the amendment corrects the claim numbers.

These objections have been **withdrawn**.

Rejections Withdrawn

Applicant's amendments, filed 26 October 2009, with respect to the rejection of claim 22 under 35 USC § 112, first paragraph, as failing to comply with the written description requirement, has been fully considered and is persuasive because the claim has been amended to delete the recitation "cytosine arabinoside," which had been considered to insert new matter into the claims. This rejection has been **withdrawn**.

Applicant's arguments, filed 26 October 2009, with respect to the rejection of claims 6-8 under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.*, in view of journal publication by Okuda *et al.*, as applied to claim 1, further in view of Remington's The Science and Practice of Pharmacy, in view of journal publication by Stuchlík *et al.*, as evidenced by online publication entitled "Carrier/Fixed Oil Profiles," has been fully considered and are persuasive because oleic acid present in vegetable oils is in the form of glycerin trioleate and not ethyl oleate. Thus, the combined teachings of the prior art do not disclose a composition comprising the riboflavin ester with ethyl oleate. This rejection has been **withdrawn**.

Applicant's arguments, filed 26 October 2009, with respect to the rejection of claim 30-32 under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.*, in view of journal publication by Okuda *et al.*, in view of Remington's The Science and Practice of Pharmacy, as applied to claims 12, 24, 25, 28 and 29, further in view of journal publication by Stuchlík *et al.*, as evidenced by online publication entitiled "Carrier/Fixed Oil Profiles," has been fully considered and are persuasive because oleic acid present in vegetable oils is in the form of glycerin trioleate and not ethyl oleate. Thus, the combined teachings of the prior art do not disclose a composition comprising the riboflavin ester with ethyl oleate. This rejection has been **withdrawn**.

In view of the cancellation of claims 2-5, 9-11 and 13-20, all rejections made with respect to claims 2-5, 9-11 and 13-20 in the previous Office Action are withdrawn. These rejections have been **withdrawn**.

The following are new grounds of rejections.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "CODPL" in claim 22 renders the claim herein indefinite. Acronyms or abbreviations can be interpreted differently depending on the context and the art. For example, "EPA" can stand for "eicosapentaenoic acid" or it can be an abbreviation for the "Environmental Protection Agency". Thus, it is unclear what "COPDL" is an abbreviation for, particularly since it is not readily apparent in the Specification. To render the claim definite, it is respectfully suggested that Applicants spell out what they intend to claim (with sufficient support in the Specification), rather than use acronyms or abbreviations.

Response to Arguments

Applicant's amendment, filed 26 October 2009, with respect to the rejection of claim 22 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been considered but is not persuasive. It is noted that the Applicant amended the claim to indicate that DA is an abbreviation only for daunorubicin and not cytosine arabinoside, further deleting the recitation "cytosine arabinoside." However, in making the amendments, the Applicant further inserted the recitation "CODPL," which again renders the claim indefinite, for reasons as described above.

Claim Rejections - 35 USC § 112, First Paragraph

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for "injecting intermuscularly." The original specification clearly discloses "intramuscular injection" in paragraph 0016 of the published application. However, intermuscular injection is not disclosed in the specification as originally filed. Adequate written description means that, in the specification, the applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the [claimed] invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 [19 USPQ2d 1111] (Fed. Cir. 1991). When no such description can be found in the specification, the only thing the PTO can reasonably be expected to do is point out its nonexistence. *In re Alton*, 76 F.3d 1168, 1175 [37 USPQ2d 1578] (Fed. Cir. 1996).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 1 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record).

Yamabe *et al.* teach the preparation of riboflavin trilaurate (abstract). It is noted that Yamabe *et al.* do not teach the positions of trilaurate esterification. However, based on the disclosed procedure, it is the Office's position that one of the esterified

positions is the 5'-OH as it is the only primary alcohol on the riboflavin chain, as compared to the remaining hydroxyl groups which are at a secondary position, and it is common knowledge to one of ordinary skill in the organic chemistry arts that a primary alcohol reacts much faster than secondary alcohols.

The teachings of Yamabe *et al.* differ from that of the instantly claimed invention in that Yamabe *et al.* teach a trilaurate ester of riboflavin whereas the claims of the instant invention is drawn to a 5'-laurate monoester of riboflavin.

Okuda *et al.* teach nutritional and ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate. To test the nutritional effects of the riboflavin derivatives, rats were fed either a standard diet, a riboflavin-deficient diet, a riboflavin-deficient diet supplemented with riboflavin-5'-monobutyrate suspended in olive oil, or a riboflavin-deficient diet supplemented with riboflavin-5'-monopalmitate suspended in olive oil (p. 9, under subheading "methods"). The authors previously showed that riboflavin tetrabutyrate had the same vitamin B_2 activity (nutritional and ariboflavinosis-curing effects) in young rats as riboflavin, but riboflavin tetrapalmitate did not have vitamin B_2 activity as rats administered riboflavin tetrapalmitate clearly showed ariboflavinosis. Similar to riboflavin tetrabutyrate, rats fed a diet supplemented with riboflavin-5'-monobutyrate exhibited vitamin B_2 activity (p. 13, second full paragraph). However, rats fed a diet supplemented with riboflavin-5'-monopalmitate showed signs of lower vitamin B_2 activity. Their results suggest that riboflavin-5'-monobutyrate is easily hydrolyzed to riboflavin, and hence has the same nutritional effect as riboflavin, while

riboflavin-5'-monopalmitate was only slowly hydrolyzed to riboflavin (p. 13, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the aribоflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate. Since Okuda *et al.* teach that riboflavin tetrapalmitate did not have vitamin B_2 activity as compared to riboflavin tetrabutyrate when fed to rats while riboflavin-5'-monopalmitate showed signs of lower vitamin B_2 activity as compared to riboflavin-5'-monobutyrate when fed to rats, one would have been motivated to modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-laurate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Okuda *et al.*, that long chain tetra-esters of riboflavin exhibited no riboflavin activity while long chain mono-esters of riboflavin exhibited some riboflavin activity. Therefore, since Okuda *et al.* also teach that the tetra- and mono-butyrate esters of riboflavin showed the same activity as riboflavin, suggesting that shorter alkyl chain esters of riboflavin are better hydrolyzed, one would have been motivated to shorten the palmitate chain to a laurate chain, such as that taught by Yamabe *et al.* However, one would further modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-monolaurate, as the teachings of Okuda *et al.* also suggest that with longer chain esters, the mono-ester compound is better hydrolyzed as compared to the tetra-ester compound, and therefore, would also

likely be better hydrolyzed as compared to the tri-ester compound taught by Yamabe *et al.*

Applicants are requested to note that the recitation "for intramuscular injection" in claim 34 is considered to be an "intended use" of the composition. The "intended use" of a composition will not further limit the claims drawn to a composition or product, so long as the prior art discloses the same composition comprising the same ingredients in an effective amount, as the instantly claimed. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments, filed 26 October 2009, and the Declaration of Mr. Xu Qishou, submitted by Applicant on 12 January 2010 under 37 CFR § 1.132, with respect to the rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.*, in view of journal publication by Okuda *et al.*, have been fully considered but are not persuasive.

Applicant argues that it would not be obvious for persons skilled in the art to select the 5'-lauric acid ester of riboflavin even though Okuda *et al.* teach the relative activity of various tetra- and monoesters of riboflavin because it is well-known that there are four –OH groups within the chemical structure of riboflavin and the esterification degrees, esterification sites, and ester-forming carboxylic acids will affect substantively

the properties of the resultant riboflavin derivatives, especially the bio-availability. Applicant further submitted a Declaration comparing the activities observed among mono-, di-, tri- and tetra-laurate esters of riboflavin, and concluded that the 5'-laurate ester exhibited superior activity compared to the other laurate ester compounds. Applicant's arguments and the Declaration of Mr. Xu have been carefully reviewed but are not deemed to be persuasive. Contrary to Applicant's assertion, the results disclosed in Figures 2-5 and Table 1 of the Declaration clearly show that the different degrees of laurate ester esterification on riboflavin does not significantly alter the properties of the compound. For example, in Figure 3 and Table 1, the body weight gain and diet intake of the rats fed the different laurate ester compounds are very similar, and even overlap, when standard deviation is taken into account. For example, rats fed the monolaurate ester (9010-I) had a diet intake of 110±15 whereas rats fed the trilaurate ester (9010-III) had a diet intake of 111±12. In another example, with regards to changes in body weight, Figure 4, for example, show no unexpected differences between rats fed the monolaurate, trilaurate or tetralaurate esters of riboflavin. Thus, since the Declaration of Mr. Xu does not show convincing data of unexpected properties between the 5'-laurate monoester of riboflavin and the di-, tri-, or tetra-laurate esters of riboflavin, the instantly claimed invention is considered *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claims 6, 12, 23-26, 29, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record) as applied to claims 1 and 34 above, further in view of Remington: The Science and Practice of Pharmacy (hereinafter referred to as Remington, PTO-892, Ref. U), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; PTO-892, Ref. A), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (PTO-892, Ref. B).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.* and Okuda *et al.* differ from that of the instantly claimed invention in that they do not expressly disclose formulation of the riboflavin ester compositions with ethyl oleate.

Remington teaches that the goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration (p. 1660, column 1, paragraph 1). Different methods of drug delivery include conventional drug therapy and nonimmediate-release drug therapy, which includes delayed release, sustained release, site-specific release and receptor release (p. 1661, column 1, paragraph 1). Sustained-release systems include any drug delivery system that achieves slow release of drug over an extended period of time (p. 1661, column 1, paragraph 30). Advantages of sustained release drug therapy are that it avoids patient compliance problems, employs less total drug, and improves efficiency in treatment (p. 1662, column 2, Table 1). The drug for

sustained release may be formulated for oral or parenteral dosage. The most common types of dosage forms used for parenteral sustained-release drug therapy are intramuscular injections, implants for subcutaneous tissues and various body cavities and transdermal devices (p. 1669, column 2, subheading "Parenteral Dosage Forms"). Intramuscular injections may be in the form of aqueous solutions, complex formation, aqueous suspensions, and oil solutions or oil suspensions (p. 1670-1671). The rate-limiting step in drug release from an aqueous suspension is dissolution (p. 1670, column 1, subheading "Aqueous Suspensions"). In the case of oil solutions, the release rate of a drug is determined by partitioning of the drug out of the oil into the surrounding aqueous medium (p. 1670, column 2, subheading "Oil Solutions and Oil Suspensions"). Drug release from oil suspensions combines the principles involved in aqueous suspensions and oil solutions. The duration of action obtained from oil suspensions is longer than that from oil solutions (p. 1671, column 1, first full paragraph). Examples of oil solutions and oil suspensions are provided in Tables 10 and 11 wherein the oil component is from sesame oil or cottonseed oil (p. 1671).

The Goldenberg '740 patent teaches the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent. The biologically active agent is incorporated into a polyol/thickened oil suspension, said biologically active agent in the form of a powder or aqueous solution, and said suspension capable of providing for the sustained-release of the biologically active agent (column 3, lines 41-47). The composition is prepared for parenteral administration to a warm blooded animal, wherein said suspension is

administered subcutaneously, or intramuscularly, and the biologically active agent is released from the suspension at a controlled rate for up to one week or more (column 3, lines 48-54). The oils used in the composition are biocompatible, of low acidity, and essentially free from rancidity, and are selected from the group consisting of sesame seed, cannola, saffron, castor, cottonseed, olive, peanut, sunflower seed, ethyl oleate, vitamin E, and Miglyol 812 (column 6, lines 57-63).

Wicks *et al.* teach long-acting antiparasitic formulations of doramectin, suitable for injection. The formulation comprises 1-11% w/v of doramectin, in a solvent comprising castor oil at about 25-80% v/v and either (i) ethyl oleate at about 20-75% v/v, or (ii) fractionated coconut oil at about 20-75% v/v, and (iii) optional further auxiliaries (paragraphs 0005-0008). The said formulation has been shown to provide efficacy against economically important endo-parasites at up to 4 months, and ecto-parasites at up to 3 months, following a single injection (paragraph 0013).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting

antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate. Since Remington teaches that advantages of sustained release drug therapy are that it avoids patient compliance problems, employs less total drug, and improves efficiency in treatment, one of ordinary skill in the art would have been motivated to formulate the riboflavin-5'-monolaurate compound, taught in the combined teachings of Yamabe *et al.* and Okuda *et al.*, into an oil suspension, such as with ethyl oleate, for sustained release, particularly since the duration of action obtained from oil suspensions is longer than that from oil solutions. Furthermore, as disclosed in the Goldenberg '740 patent and the teachings of Wicks *et al.*, formulation of a biologically active compound with oils, such as ethyl oleate, results in a prolonged release of the injectable suspension that would provide efficacy from up to one week to up to four months.

With regards to the limitation wherein the drug is administered to an animal that is a human, it is common practice in the pharmaceutical arts to first test drugs in animals, such as rats, before application to humans. Thus, successful *in vivo* testing in rats would marshal resources and direct the expenditure of effort to human clinical trials of the successful compounds, thereby providing an immediate benefit to the public. This is considered to be analogous to the benefit provided by the showing that a drug has *in vivo* utility (see MPEP § 2107.01).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments, filed 26 October 2009, and the Declaration of Mr. Xu Qishou, submitted by Applicants on 12 January 2010 under 37 CFR § 1.132, with respect to the rejection of claims 6-8 and 30-32 under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.*, in view of journal publication by Okuda *et al.*, further in view of Remington's The Science and Practice of Pharmacy, in view of journal publication by Stuchlík *et al.*, as evidenced by online publication entitled "Carrier/Fixed Oil Profiles," and the rejection of claims 12, 24, 25, 28 and 29 under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.*, in view of journal publication by Okuda *et al.*, further in view of Remington's The Science and Practice of Pharmacy, have been fully considered and are moot in view of the modified/new ground of rejection above and in section [0003] below.

Specifically, Applicant argues that the composition of the riboflavin ester in a composition with ethyl oleate provides an unexpected long-acting property wherein the compound could remain effective for three months after intramuscular injection. The Applicant additionally argues that the specific combination of 5'-lauric acid ester of riboflavin and ethyl oleate, optionally with camellia oil, would be unduly burdensome for one of ordinary skill in the arts to find from among the numerous known pharmaceutically acceptable solvents. This argument is not persuasive because Remington, the Goldenberg '740 patent, Wicks *et al.*, and the Holl '650 patent, separately, and in combination, teach that it is well known to one of ordinary skill in the arts that oil suspensions, such as the formulation of a drug with ethyl oleate, results in a

prolonged release of the injectable suspension with efficacy from up to one week to up to four months. Furthermore, formulation of a drug with a suitable carrier is considered to be routine in the pharmaceutical arts.

Applicant further argued unexpected results and submitted a Declaration comparing the activities observed among mono-, di-, tri- and tetra-laurate esters of riboflavin, and concluded that the 5'-laurate ester exhibited superior activity compared to the other laurate ester compounds. As discussed in the "Response to Arguments" section in section [0001] above, the Declaration of Mr. Xu does not convincingly show any unexpected properties between the 5'-laurate monoester of riboflavin and the di-, tri-, or tetralaurate esters of riboflavin. Thus, the instantly claimed invention is considered *prima facie* obvious over the combined teachings of the prior art.

Applicant also argues that the specifically selected compound, 5'-lauric acid ester of riboflavin, is unobvious over riboflavin compounds of varying chain lengths because of unexpected effects. This argument is not persuasive since Okuda *et al.* already disclose that a 5'-monoester of 16 carbons in length (palmitate) exhibit some, albeit reduced, riboflavin activity. Thus, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute known shorter chain esters of riboflavin, such as laurate esters (12 carbons in length) of riboflavin, which is taught by Yamabe *et al.* Applicant's arguments of unexpected effects are not persuasive absence any evidence. Applicant is requested to note that the Declaration submitted to show unexpected results only disclose difference in degrees of esterification, which the Office considers not to be unexpected in view of the similar activity observed between the riboflavin

esters varying in their degree of esterification. However, there was no evidence of unexpected results provided in the Declaration for 5'-monoesters varying in the carbon chain length, such as unexpected results of the instantly claimed 5'-laurate monoester as compared to the 5'-butyrate and 5'-palmitate monoesters of riboflavin. Thus, absence any unexpected results to the contrary, the instantly claimed invention is *prima facie* obvious over the combined teachings of the prior art.

Section [0003]

Claims 7, 8, and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record) as applied to claims 1 and 34 above, further in view of Remington: The Science and Practice of Pharmacy (hereinafter referred to as Remington; PTO-892, Ref. U), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; PTO-892, Ref. A), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (PTO-892, Ref. B), as applied to 6, 12, 23-26, 29, 30, further in view of U.S. Patent No., 5,554,650 to Holl *et al.* (hereinafter referred to as the '650 patent; PTO-892, Ref. C).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Remington, the Goldenberg '740 patent, and Wicks *et al.* were as described in section [0002] above of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.*, Okuda *et al.*, Remington, the Goldenberg '740 patent, and Wicks *et al.* differ from that of the instantly claimed invention in that the combined teachings of the prior art do not expressly disclose a composition comprising the 5'-lauric acid ester of riboflavin with camellia oil, or a method of treating ariboflavinosis comprising administering the same composition.

The Holl '650 patent teaches an antiphlogistic, analgesic, antipyretic parenteral preparation comprising diclofenac, its salt, or both, a surfactant, cosurfactant, water, and optionally comprising an oily component, that can exhibit sustained therapeutic levels of diclofenac in plasma (column 1, lines 6-14, lines 60-67). Incorporation of an oily component in the parenteral preparation decreases the peak plasma concentration of diclofenac or its salt after administration, increases the time to achieve peak plasma concentration of diclofenac or its salt after administration, and prolongs the period of time for which diclofenac or its salt remains active (column 3, lines 18-26). One or more oily components can be selected from the group consisting of glycerin fatty acid esters, fatty acid esters, and hydrocarbons (column 3, lines 27-30). Preferred are glycerin fatty acid esters that are almond oil, olive oil, sesame oil, peanut oil, fennel oil, camellia oil, corn oil, castor oil, cotton seed oil, and soybean oil, which may be used alone or in combination with one or more oily components (column 3, lines 34-41). The oily components may be incorporated into the parenteral preparation in an amount of about 0.5-30 wt%, preferably 1-15 wt% (column 3, lines 44-47).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate,

with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of the Holl '650 patent, regarding incorporation of an oily component into a parenteral diclofenac preparation to prolong its period of activity after administration. Since Remington teaches that advantages of sustained release drug therapy are that it avoids patient compliance problems, employs less total drug, and improves efficiency in treatment, one of ordinary skill in the art would have been motivated to formulate the riboflavin-5'-monolaurate compound, taught in the combined teachings of Yamabe *et al.* and Okuda *et al.*, into an oil suspension, such as with ethyl oleate, for sustained release, particularly since the duration of action obtained from oil suspensions is longer than that from oil solutions. Furthermore, as disclosed in the Goldenberg '740 patent and the teachings of Wicks *et al.*, formulation of a biologically active compound with oils such as ethyl oleate results in a prolonged release of the injectable suspension that would provide efficacy from up to one week to up to four months. Since the Holl '650 patent also teaches that oily components prolong the period at which an administered drug remains active, similar to

Remington, the Goldenberg '740 patent, and Wicks *et al.*, and further teaches that the oily components can be used in combination with each other, one of ordinary skill in the art would have been further motivated to include additional oily components into the composition, with the expectation that the sustained delivery of the active drug would be maintained. Furthermore, as Remington teaches that the release rate of a drug in an oil solution is determined by partitioning of the drug out of the oil into the surrounding aqueous medium, and the release rate of a drug in an oil suspension is determined by the same factor as an oil solution as well as dissolution of the drug in an aqueous solution, one of ordinary skill in the art would conclude that the different properties of the oily components would affect the release rate of the drug, and thus, different combinations of the oily components, such as ethyl oleate and camellia oil, in different amounts, would also affect the release rate of the drug. As such, based on the combined teachings of the prior art, one of ordinary skill in the art would be able to make various compositions of riboflavin-5'-monobutyrate in different oily components, in different concentrations, depending on the desired rate of drug release.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0004]

Claims 21, 22 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record) as applied to claims 1 and 34 above, further in

view of Remington: The Science and Practice of Pharmacy (hereinafter referred to as Remington; PTO-892, Ref. U), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; PTO-892, Ref. A), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (PTO-892, Ref. B), as applied to 6, 12, 23-26, 29, 30, further in view of PG Pub No. US 2003/0105104 A1 by Burzynski (of record), in view of journal publication by McCarthy *et al.* (of record).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Remington, the Goldenberg '740 patent, and Wicks *et al.* were as described in section [0002] above of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.*, Okuda *et al.*, Remington, the Goldenberg '740 patent, and Wicks *et al.* differ from that of the instantly claimed invention in that the combined teachings of the prior art teach administration of riboflavin-5'-monolaurate for treatment of ariboflavinosis and not for the treatment of digestive tract catarrh caused by bone marrow transplantation, leukemia or chemotherapy.

Burzynski teaches a pharmaceutical composition comprising riboflavin, effectors of the urea cycle, and amino acids, suitably combined with appropriate carriers, diluents, or excipients (abstract; paragraph 0001 and 0008; claim 14), as well as a method for alleviating or reducing the toxic, nutritional and metabolic disturbances associated with cancer and cancer chemotherapy by administering the said composition to a cancer patient in need thereof (paragraph 0024; claim 1). Common side effects

associated with cancer treatment include tiredness, loss of appetite, mucositis, diarrhea and myelosuppression (paragraph 0072). In example 1 (paragraphs 0070-0073), Burzynski shows that when a female patient diagnosed with adenocarcinoma of the colon was administered a composition comprising a sterile solution of six amino acids, L-arginine, and riboflavin prior to treatment by chemotherapy with methotrexate and 5-fluorouracil, the patient did not experience the side effects typically associated with the chemotherapy treatment.

McCarthy *et al.* teach risk factors associated with mucositis in patients receiving 5-fluorouracil chemotherapy for cancer of the digestive tract. Oral mucositis is a dose-limiting toxicity of 5-fluorouracil and includes inflammation and ulceration of the oral mucosa and myelosuppression (abstract; p. 484, column 2). Although no direct relationship could be drawn, their results suggest that a lower neutrophil count is associated with the development of oral mucositis during therapy (p. 488, column 2, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the

biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of Burzynski, regarding a pharmaceutical composition comprising riboflavin, effectors of the urea cycle and amino acids, with the teachings of McCarthy *et al.*, regarding the risk factors associated with mucositis in patients receiving 5-fluorouracil chemotherapy for cancer of the digestive tract catarrh. Since McCarthy *et al.* teach that as digestive tract catarrh is a risk factor of patients undergoing chemotherapy and Burzynski teach that riboflavin can alleviate the toxicity associated with a chemotherapy regimen, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the riboflavin compound taught by Burzynski with a riboflavin ester, such as riboflavin-5'-monolaurate, as taught in the combined teachings of Yamabe *et al.* and Okuda *et al.*, with the expectation that riboflavin-5'-monolaurate would treat digestive tract catarrh caused by chemotherapy. It is noted that the Burzynski reference does not specifically teach the administration of ester analogs of riboflavin to cancer patients exhibiting the common side effects of chemotherapy. However, as described above in section [0001] of the claim rejections under 35 USC § 103, Okuda *et al.* teach that esters of riboflavin can be hydrolyzed to the natural riboflavin compound and thus exhibit activity similar to riboflavin. Therefore, esters of riboflavin, such as the 5'-laurate monoester of riboflavin, can serve as functional substitutes for natural riboflavin when administered in a composition. Furthermore, it would have *prima facie* obvious to one of ordinary skill in that art that the enhanced lipophilicity of the riboflavin ester due to the presence of the

alkyl chain would enhance its migration through lipid bilayers of cells, and thus its bioavailability.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0005]

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record) as applied to claims 1 and 34 above, further in view of Remington: The Science and Practice of Pharmacy (hereinafter referred to as Remington; PTO-892, Ref. U), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; PTO-892, Ref. A), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (PTO-892, Ref. B), as applied to 6, 12, 23-26, 29, 30, further in view of U.S. Patent No. 6,565,891 to Chandra (herein referred to as the '891 patent, of record).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Remington, the Goldenberg '740 patent, and Wicks *et al.* were as described in section [0002] above of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.*, Okuda *et al.*, Remington, the Goldenberg '740 patent, and Wicks *et al.* differ from that of the instantly claimed invention in that the combined teachings of the prior art teach administration of

riboflavin-5'-monolaurate for treatment of ariboflavinosis and not for the treatment of persistent oral ulcer.

The Chandra '891 patent teaches a nutritional supplement for children that is most effective in optimizing health, increasing the immunity, and decreasing the instances and severity of infection, particularly among children (abstract). The importance of each of the component vitamins and minerals making up the nutritional supplement is described in detail. Of particular relevance, is the importance of riboflavin in the nutritional supplement. The Chandra '891 patent teaches that riboflavin participates in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the respiratory chain (column 7, lines 22-31). It is used therapeutically to ameliorate ariboflavinosis resulting from diverse causes such as inadequate dietary intake, decreased assimilation, rare genetic defects in the formation of specific flavoproteins, hormonal disorders and after use of certain drugs. Symptoms indicating riboflavin deficiency include rough skin, angular stomatitis, cracked lips, and mouth ulcers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened

oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of the Chandra '891 patent, regarding the various symptoms of riboflavin deficiency. Since the Chandra '891 patent teaches that oral ulcers are a symptom of riboflavin deficiency, it is the Office's position that the patient population being treated for ariboflavinosis with a riboflavin ester would necessarily overlap with the patient population that has oral ulcers, and thus would be treated using the same methods.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Eremin *et al.* (PTO-892, Ref. V) discloses a study on replacing vegetable oils in parenteral drugs with ethyl oleate.

No claim is allowed. This rejection is made NON-FINAL due to the new/modified grounds of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-

270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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